The Office Action asserts that claims 24 and 25 are indefinite because one skilled in the art allegedly would not know how to identify the "biological activity against" or how to identify the "disease or disorder" when the claim is allegedly directed to an unspecified disease caused by an unspecified organism or cause. Applicants have amended the claims to remove any unintended ambiguity and render the claims even more clear. Applicant respectfully points out that the description of the invention is the role of the specification, not the claims. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.,* 1 U.S.P.Q.2d 1081 (Fed. Cir. 1986). In addition, the amount of detail required to be included in the claims is not to be viewed in the abstract but in conjunction with the specification. *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.,* 225 U.S.P.Q. 634 (Fed. Cir. 1985). Indeed, Applicants teach at, for example, page 33, lines 10-27 of the specification that "having biological activity" means that the nucleic acid functions to modulate the expression of one or more genes in an animal as reflected in either absolute function of the gene (such as ribozyme activity) or by production of proteins coded by such genes. Thus, Applicants do, in fact, provide a definition of the objected phrase. Further, one skilled in the art is familiar with diseases caused by eukaryotic pathogens, retroviruses, and non-retroviral viruses. Applicants also disclose numerous miscellaneous diseases, diseases caused by eukaryotes, retroviruses, and non-retroviruses in Tables 3, 4, 5, and 6, respectively. Persons of ordinary skill would have no difficulty in determining whether a given disease meets the criteria recited in the claim. Accordingly, claims24 and 25 are definite within the meaning of § 112. *In re Mercier*, 185 U.S.P.Q. 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one skilled in the art can determine what subject matter is or is not within the scope of the claims). The Office Action does not dispute that one skilled in the art would be able to identify other disorders, diseases resulting from eukaryotic pathogens, retroviruses including HIV or non-retroviral viruses. Further, the Examiner has failed to provide any reasoning why one skilled in the art would not be able to determine whether a particular oligonucleotide has biological activity against those disorders, diseases resulting from eukaryotic pathogens, retroviruses including HIV or non-retroviral viruses explicitly recited in Applicants'

specification or any other disorders or diseases. Accordingly, Applicants respectfully request that the rejection of claims 24 and 25 under 35 U.S.C. § 112, second paragraph, be withdrawn.

III. The Claimed Inventions Are Enabled

Claims 1-40 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable the claimed invention. Applicants respectfully request reconsideration of this rejection since one skilled in the art would be able to practice the claimed inventions without being required to perform undue experimentation.

As will be recognized, the enablement requirement of § 112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under § 112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must*** be taken as in compliance with the enabling requirements of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. (emphasis added)

For sake of clarity, Applicants have addressed this rejection in sections directed to i) pharmaceutical compositions (claims 1-24 and 31-39) and methods of investigating the role of a gene or gene

product (claims 28-30), and ii) methods of treatment (claims 25-27) and methods of modulating gene expression (claim 40).

Regarding the claims directed to pharmaceutical compositions and methods of investigating the role of a gene or gene product, no evidence or reasoning substantiating the doubts so expressed regarding enablement thereof have been provided. See, *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974). The Examiner is reminded that Applicants need only enable one use for such compositions and that **any utility** that Applicants enable for the claimed pharmaceutical compositions is sufficient for purposes of enablement. The Examiner is reminded that pharmaceutical compositions can have utilities in addition to treatment including, for example, *in vitro* and *in vivo* applications.

Applicants provide numerous uses for the claimed pharmaceutical compositions which are enabled. For example, Applicants teach at page 33, lines 28 to page 34, line 8, of the specification that the claimed compositions can be used to study the function of one or more genes in animals other than humans. In support of this enabled use, Applicants cite at pages 33-34 several scientific publications evidencing use of antisense oligonucleotides in such a manner. Applicants also cite a scientific publication at page 34 which show the use of antisense oligonucleotides as "antisense knockouts." The Office Action fails to provide any evidence or reasoning to support the erroneous conclusion that a pharmaceutical composition comprising a nucleic acid and a penetration enhancer cannot be used to, for example, study the role of the N-methyl-D-aspartate receptor in neuronal death, investigate the biological role of protein kinase C-α, to examine the role of the neuropeptide Y1 receptor in anxiety, and as antisense knockout agents. Accordingly, Applicants teach one skilled in the art to use the claimed pharmaceutical compositions to, *inter alia*, study the function of one or more genes in an animal. No undue amount of undue experimentation is required in order to use the claimed compositions according to the published references cited by Applicants. Thus, the compositions and methods set forth in claims 1-24 and 28-39 are enabled.

In regard to the claims directed to methods of treatment and methods of modulating gene expression, the Office Action admits at page 5 that:

> [T]he Specification does provide teaching on the introduction of nucleic acids into the blood and generally into the organs of an animal via the enteral pathway which is a step toward a pharmaceutical treatment with nucleic acids...

Thus, the Office Action does not dispute and, in fact, acknowledges that Applicants, at a minimum, provide an enabling disclosure teaching one skilled in the art to introduce nucleic acids via the enteral pathway into the blood and organs of an animal. The Office Action erroneously concludes, however, that the claimed compositions would have no therapeutic effect upon reaching the bloodstream, listing several Wands factors allegedly in support of the Examiner's position. The theme of these Wands factors is that since pharmaceutical treatment with antisense oligonucleotides is a new and developing art, Applicants' claimed invention is unpredictable. Antisense oligonucleotides have been administered to animals, however, since the late 1970's and, thus, is not new. Furthermore, all medicinal arts are developing, even those that have been around for decades, *i.e.*, antibiotics. In addition, extraneous issues such as mechanism of action and side effects are irrelevant to whether the claimed inventions are enabled. As outlined below, one skilled in the art would be able to practice the claimed invention without being required to perform any amount of undue experimentation.

Applicants teach at page 2, lines 5-13 of the specification that oligonucleotides have been shown to be effective for the treatment of diseases and/or disorders. For example, Robertson, *Nature Biotechnology*, **1997**, *15,* 209 and Anon, *Genetic Engineering News*, **1997**, *15*, 1 each discuss successful treatment of Crohn's disease via intravenous infusions of antisense oligonucleotides. In addition, Applicants enclose herewith copies of 1) Monia *et al.*, *Nature Med.*, **1996**, *2*, 668, 2) Oberbauer *et al.*, *Proc. Natl. Acad. Sci. USA*, **1996**, *93*, 4903, 3) Monia *et al.*, *Proc. Natl. Acad. Sci. USA.*, **1996**, *93*, 15481, 4) Cucco *et al.*, *Cancer Res.*, **1996**, *56*, 4332, 5) Offensperger *et al.*, Antisense Therapy of Hepatitis B Virus Infection, **1996**, Agrawal Ed., Humana Press Inc. Tolowa, NJ, pp. 143-158, 6) Sun *et al.*, *Br. J. Pharmacol.*, **1996**, *118*, 131, 7) Neurath *et al.*, *Nature Med.*, **1996**, *2*, 998-1004, 8) Leonetti *et al.*, *J. N.C.I.*, **1996**, *88*, 419, and 9) Del Bufalo *et al.*, *Br. J. Cancer*, **1996**, *74*, 387, each of which demonstrate successful administration of pharmaceutical nucleic acids

via the bloodstream or local administration, which was the state of the art at the time of Applicants' invention. Each of these references shows that oligonucleotides administered to the bloodstream, in fact, reach their target destinations as well as have their intended effects on the target. Since the Office Action admits that Applicants enable one skilled in the art to introduce nucleic acids into the blood and generally into the organs of an animal via the enteral pathway and since the state of the art at the time the application was filed demonstrates that oligonucleotides administered into the blood reach their intended target and have, for example, anti-tumor activity, the claimed invention is enabled. Further, since nucleic acids that have been shown to have at least some therapeutic value, pharmaceutical compositions comprising penetration enhancers and the nucleic acids are also enabled. Thus, one skilled in the art is not required to perform any amount of undue experimentation in order to practice the claimed invention.

In view of the foregoing, Applicants respectfully request that the rejection of claims 1-40 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Conclusion

It is respectfully submitted that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested.

Respectfully submitted,

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